ORIGINAL RESEARCH

Characteristics and Treatment Outcomes of Acute Type A Aortic Dissection With Elevated D-Dimer Concentration

Ryo Itagaki, MD; Naoyuki Kimura, MD, PhD; Makiko Mieno, PhD; Daijiro Hori, PhD; Satoshi Itoh, MD, PhD; Kei Akiyoshi, MD; Koichi Yuri, MD, PhD; Keisuke Tanno, MD; Koji Kawahito, MD, PhD; Atsushi Yamaguchi, MD, PhD

***Background*—**Clinical characteristics and treatment outcomes of acute type A aortic dissection with D-dimer elevation have not been clarified.

***Methods and Results*—**D-dimer was measured preoperatively within 24 hours of symptom onset in 262 patients with acute type A aortic dissection. The median (and interquartile range) admission D-dimer concentration in our total patient group was 26.7 (8.3–85.9) μg/mL. Median (interquartile range) D-dimer concentrations were 5.0 (2.6–18.0) μg/mL for complete false lumen thrombosis (n=33), 60.9 (19.4–160.4) μg/mL for partial thrombosis (n=81), 26.5 (10.0–70.6) μg/mL for a patent false lumen (n=131), and 8.7 (3.2–26.9) μg/mL for ulcerlike projection (n=17) (P<0.01). With a D-dimer concentration of ≤8.3 μg/mL representing the lower quartile, we then investigated predictors of a low D-dimer level. Multivariate analysis showed dissection limited to the ascending aorta (P<0.01; odds ratio, 9.81) or descending aorta (P<0.01; odds ratio, 7.68), a completely thrombosed false lumen (P<0.01; odds ratio, 4.02), and absence of brain ischemia (P=0.013; odds ratio, 4.74) to be predictors of the lower D-dimer concentration. Compared with patients with a low D-dimer concentration (≤8.3 μg/mL, n=66), patients with a D-dimer concentration >8.3 μg/mL (n=196) had a reduced preoperative platelet count and increased operation time and transfusion volume. In-hospital mortality was elevated in this group (1.5% versus 11.2%; P=0.031), although 7-year survival did not differ for hospital survivors (lower versus higher, 93.1% versus 79.1%; P=0.21).

***Conclusions*—**D-dimer concentrations are strongly influenced by the extent of dissection and false lumen status. Operative risks are increased in patients with a relatively high D-dimer concentration. **(*J Am Heart Assoc*. 2018;7:e009144. DOI: 10.1161/JAHA.118.009144.)**

Key Words: aortic dissection • D-dimer • false lumen

Acute aortic dissection (AAD) remains a life-threatening condition. Although outcomes of surgery for acute type A aortic dissection (ATAAD) have improved,[1] according to the latest International Registry of Acute Aortic Dissection–based study, in-hospital mortality among patients who have undergone aortic repair for ATAAD is ≈18%.[2] Not only are further improvements in comprehensive perioperative management needed, greater insight into the prognosis of AAD is also needed for optimization of treatment strategies. We have believed that early outcome prediction could be derived from patients' characteristics and presenting symptoms.

D-dimer elevation is seen in patients with ATAAD. D-dimer is a fibrin fragment, and its elevation is induced by the coagulation cascade and associated with fibrinolysis.[3] D-dimer is now commonly measured not only following fibrinolytic therapy but also in the diagnosis of various diseases, including pulmonary embolism, disseminated intravascular coagulation, sepsis, malignancy, and acute myocardial infarction.[4,5] The utility of D-dimer assessment in the diagnosis of acute aortic syndrome, including AAD, is well recognized.[6–10] The European Society of Cardiology Guidelines recommends D-dimer elevation as a IIa indication for a diagnostic workup of acute aortic syndrome,[11] and previously reported studies have shown correlation between D-dimer concentrations and the extent of aortic dissection.[12–14] In

From the Departments of Cardiovascular Surgery (R.I., N.K., S.I., K.A., D.H, K.Y., A.Y.) and Radiology (K.T.), Saitama Medical Center, Jichi Medical University, Saitama, Japan; Department of Medical Informatics, Center for Information, Jichi Medical University, Tochigi, Japan (M.M.); and Division of Cardiovascular Surgery, Department of Surgery, Jichi Medical University, Shimotsuke, Japan (K.K.).

Accompanying Tables S1, S2 and Figure S1 are available at http://jaha.ahajournals.org/content/7/14/e009144/DC1/embed/inline-supplementary-material-1.pdf

Correspondence to: Naoyuki Kimura, MD, PhD, Department of Cardiovascular Surgery, Saitama Medical Center, Jichi Medical University, 1-847 Amanumacho, Omiya-ku, Saitama 330-8503, Japan. E-mail: kimura-n@omiya.jichi.ac.jp

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Clinical Perspective

What Is New?

- In patients who underwent aortic repair for acute type A aortic dissection, admission D-dimer concentrations are influenced by both extension of dissection and status of false lumen.
- D-dimer concentration is relatively high in patients with a partially thrombosed false lumen and low in patients with a completely thrombosed false lumen or an ulcerlike projection–type false lumen, regardless of the extent of dissection.
- A high admission D-dimer concentration appears to be associated with a decreased platelet count, increased operative blood loss and transfusion volume, and prolonged operation time, which may increase operative mortality.

What Are the Clinical Implications?

- Operative risks are increased in patients with a relatively high D-dimer concentration.
- Recognition of the clinical and morphologic features in the context of D-dimer testing can lead to accurate diagnosis and help surgeons optimize the perioperative management of patients with acute type A aortic dissection.

addition, the D-dimer concentration is reported to be lower in patients with a thrombosed false lumen (FL) or intramural hematoma than in patients with patent-type AAD (ie, AAD with a patent FL).[12,15] Status of the FL has recently attracted attention as a predictor of late outcomes not only in patients with acute type B aortic dissection[16,17] but also in patients who undergo urgent aortic repair for ATAAD.[18,19] However, the relation between status of the FL, particularly partial thrombosis of the FL, and the D-dimer concentration in patients with AAD is poorly understood.

We conducted a retrospective study in which we investigated admission D-dimer concentrations in relation to dissection morphologic features in patients who had undergone urgent aortic repair for ATAAD and then investigated admission D-dimer concentrations in relation to early and late outcomes among these patients to determine whether admission D-dimer can be used as an early indicator of prognosis.

Methods

The Institutional Review Board of Saitama Medical Center, Jichi Medical University (Saitama, Japan), approved the study (approval No. S16-100), and the requirement for informed consent was waived. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Patients and Study Design

The study included 262 patients (143 men and 119 women; mean age, 64.5 years) who had undergone urgent or emergency surgery for ATAAD and in whom D-dimer had been measured on admission. These 262 patients were identified from among 321 patients who had undergone aortic repair for ATAAD at Saitama Medical Center, Jichi Medical University, between November 1, 2009 and October 31, 2016. The ATAAD had been diagnosed by means of contrast-enhanced computed tomography (CT). D-dimer had been measured at the time of admission in 288 of the 321 patients, but 26 of these 288 patients were hospitalized >24 hours after symptom onset. Because we wanted to control for delayed admission, we excluded these patients from the study. Thus, the study group comprised patients treated for ATAAD within 24 hours of symptom onset.

Serum D-dimer had been measured by turbidimetric immunoassay (Nanopia D-dimer; Daiichi Pure Chemicals, Tokyo, Japan) used with a monoclonal antibody (Sekisui Medical, Tokyo, Japan; detection limit, <1 μg/mL).[20]

We first investigated admission D-dimer concentrations in relation to 2 morphologic variables: the extent of dissection and status (patency) of the FL. Results of recent studies have indicated that an admission D-dimer concentration >5 to 9 μg/mL is useful in predicting early and late outcomes of AAD.[21–23] On the basis of the D-dimer distribution among our patients (Figure 1), we defined a D-dimer concentration within the lower quartile of ≤8.3 μg/mL as a low concentration, and we investigated the characteristics of patients with a low concentration. We then divided patients into 2 groups on the basis of their admission D-dimer concentration, whether ≤8.3 or >8.3 μg/mL, and compared early outcomes (in-hospital mortality and morbidity) and late outcomes (survival and aortic event-free survival) between the 2 groups. An aortic event was defined as reoperation, redissection, aortic rupture, or sudden death. Clinical information, including comorbidities and medical history, was obtained from patients' hospital records.

Morphologic Classification of Aortic Dissection

The aortic dissection was classified morphologically for all study patients on the basis of preoperative contrast-enhanced CT images. The CT images were checked independently by an experienced radiologist (K.T.) and a cardiovascular surgeon (R.I. or N.K.), and the morphologic class was assigned by consensus. Because of the urgency of the surgical treatment, CT was not routinely performed preoperatively for patients

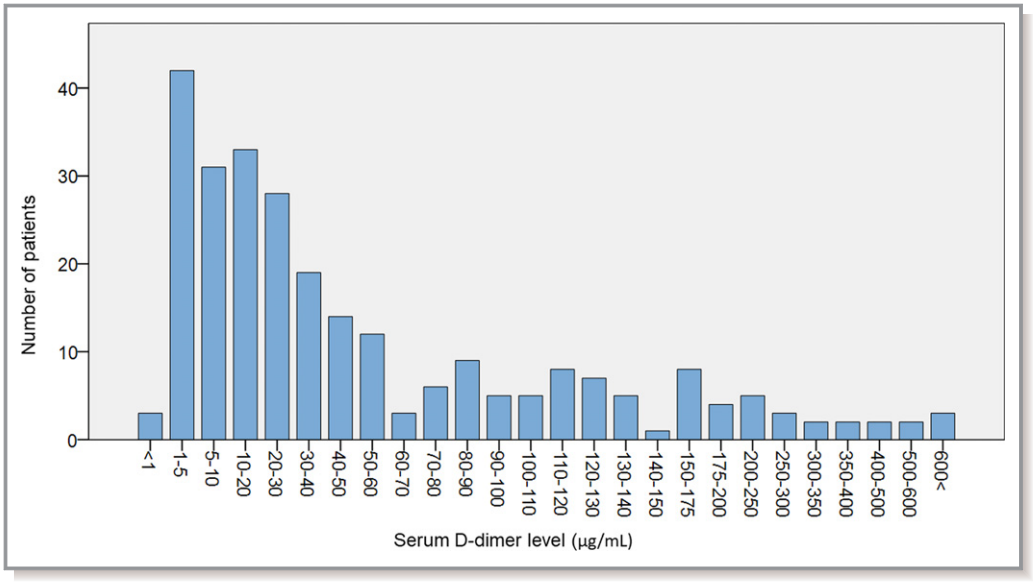

Figure 1. Distribution of admission serum D-dimer concentrations.

who had undergone contrast-enhanced CT before being referred to us. FL patency was judged on the basis of delayed-phase CT data in 239 patients. In the remaining 23 patients (9%), FL patency was judged on the basis of early-phase CT data because of lack of delayed-phase CT data.

The extents of dissection are illustrated in Figure 2A, and patients were divided into groups accordingly: those with dissection limited to the ascending aorta (DeBakey type II dissection, n=23) or to the descending thoracic aorta (n=51) and those with dissection extending to the abdominal aorta (n=71) or to one or both iliac arteries (n=117). FL statuses, as seen on CT images, are shown in Figure 2B, and patients were divided into groups accordingly.[24] The FL was judged to be completely thrombosed (n=33), partially thrombosed (n=81), patent (absence of thrombosis in the FL) (n=131), or thrombosed with a small intimal tear, observed on CT as an ulcerlike projection (ULP) (n=17).

Surgical Procedure

Surgery for ATAAD was as reported previously.[25–27] Briefly, aortic repair was performed via median sternotomy.

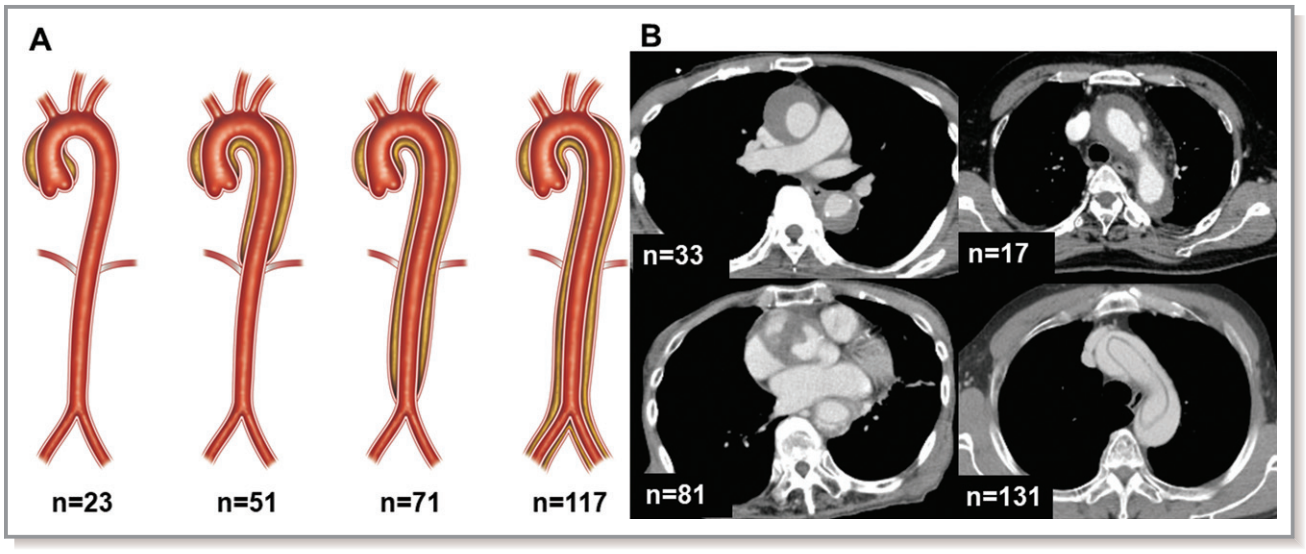

Figure 2. Morphologic classification of aortic dissection on the basis of preoperative contrast-enhanced computed tomography (CT). A, Dissection was classified by its extent as limited to the ascending aorta, limited to the thoracic descending aorta, extending to the abdominal aorta, or extending to one or both iliac arteries. B, The false lumen (FL) was classified as completely thrombosed (top left), thrombosed with an ulcerlike projection (ULP) (top right), partially thrombosed (bottom left), or patent (bottom right). Partial thrombosis appeared on the CT image as contrast medium or thrombosis anywhere in the FL (but not including the ULP).

Cardiopulmonary bypass was established with a single or multiple arterial cannulation sites. The femoral artery, axillary artery, heart apex, or ascending aorta was used for arterial inflow. Cardiopulmonary bypass was established, and systemic cooling to a rectal temperature of 20°C to 25°C was begun. The extent of distal aortic resection was determined on the basis of the location of the entry tear, aortic diameter, and the FL status in the downstream aorta. Some patients with true lumen narrowing in the downstream aorta underwent total arch replacement performed by the frozen elephant trunk technique. Selective antegrade cerebral perfusion was used in cases of total or partial (reconstruction of 1 or 2 branches) arch replacement. Distal anastomosis was performed in an open manner. The proximal stump was trimmed and reinforced with Teflon felt. Glue (fibrin glue or BioGlue) was used in some patients, according to the surgeon's preference. No gelatin-resorcinol-formaldehyde-glutaraldehyde glue was used. Modified non–valve-sparing Bentall aortic root replacement or valve-sparing reimplantation was performed in patients with aortic root dilation or an intimal tear at the root level.

Statistical Analysis

Data are shown as the number (and percentage) of patients, as median values (and interquartile range), or as mean±SD. D-dimer concentrations were evaluated in relation to morphologic class, extent of dissection, and FL status, and differences between patient groups were analyzed by Kruskal-Wallis test. Multivariate stepwise forward logistic regression analysis was used to assess independent predictors of a low D-dimer concentration (≤8.3 μg/mL) and of in-hospital mortality. The following clinical and morphologic variables were included in the multivariate logistic regression analysis: age, female sex, Marfan syndrome, bicuspid aortic valve, obesity (body mass index, >30 kg/m^2), current smoking, hypertension, dyslipidemia, diabetes mellitus, chronic obstructive pulmonary disease, hemodialysis, prior cardiac surgery, history of coronary artery disease, history of cerebrovascular disease, severe aortic insufficiency, shock (systolic blood pressure, <80 mm Hg), organ ischemia (brain, coronary, spinal, visceral, or lower limb), location of the entry tear, extent of dissection limited to the

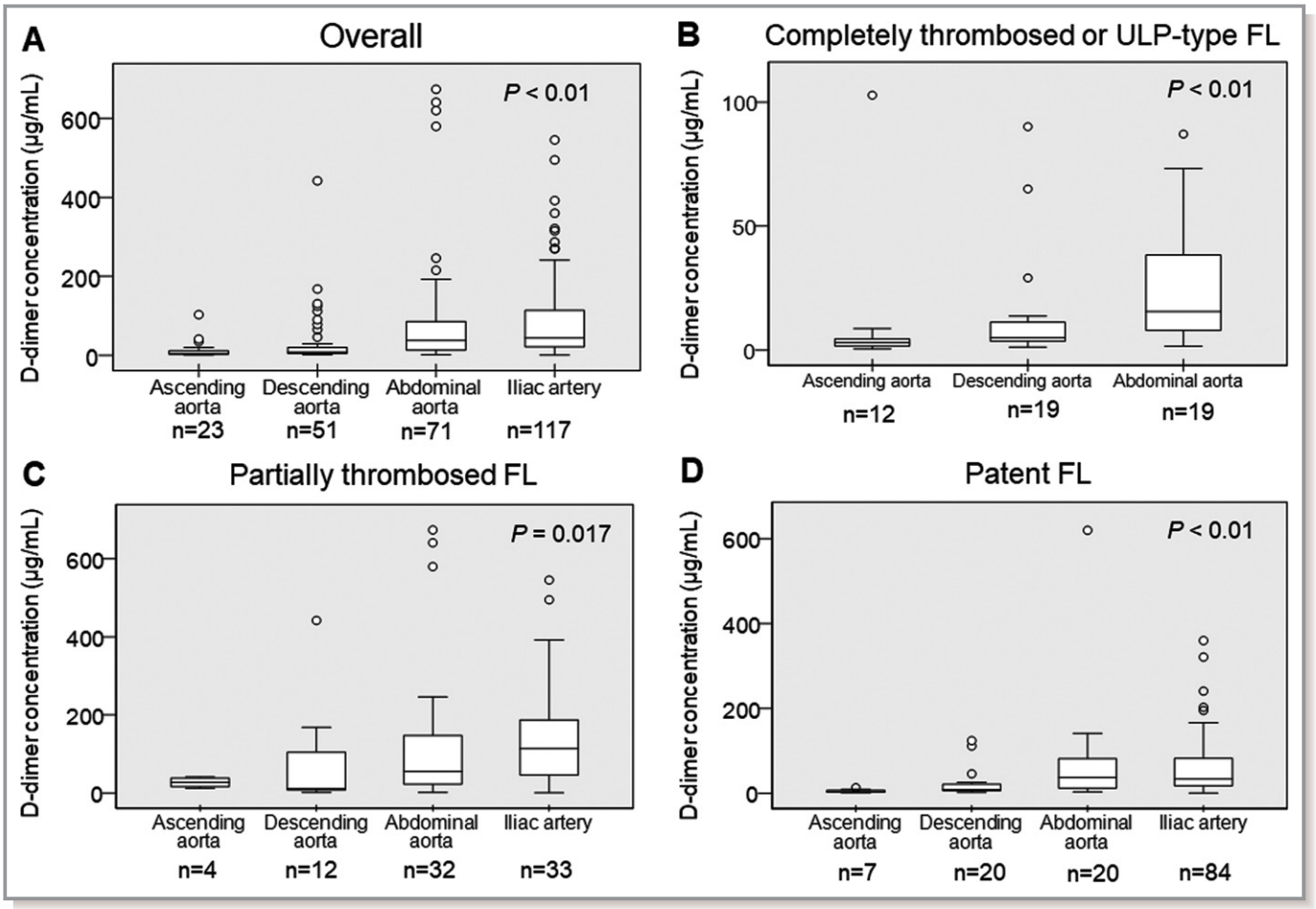

Figure 3. D-dimer concentrations assessed according to the extent of aortic dissection. A, Total patients. B through D, Patient subgroups on the basis of false lumen (FL) status. *P* values were obtained by Kruskal-Wallis test. ULP indicates ulcerlike projection.

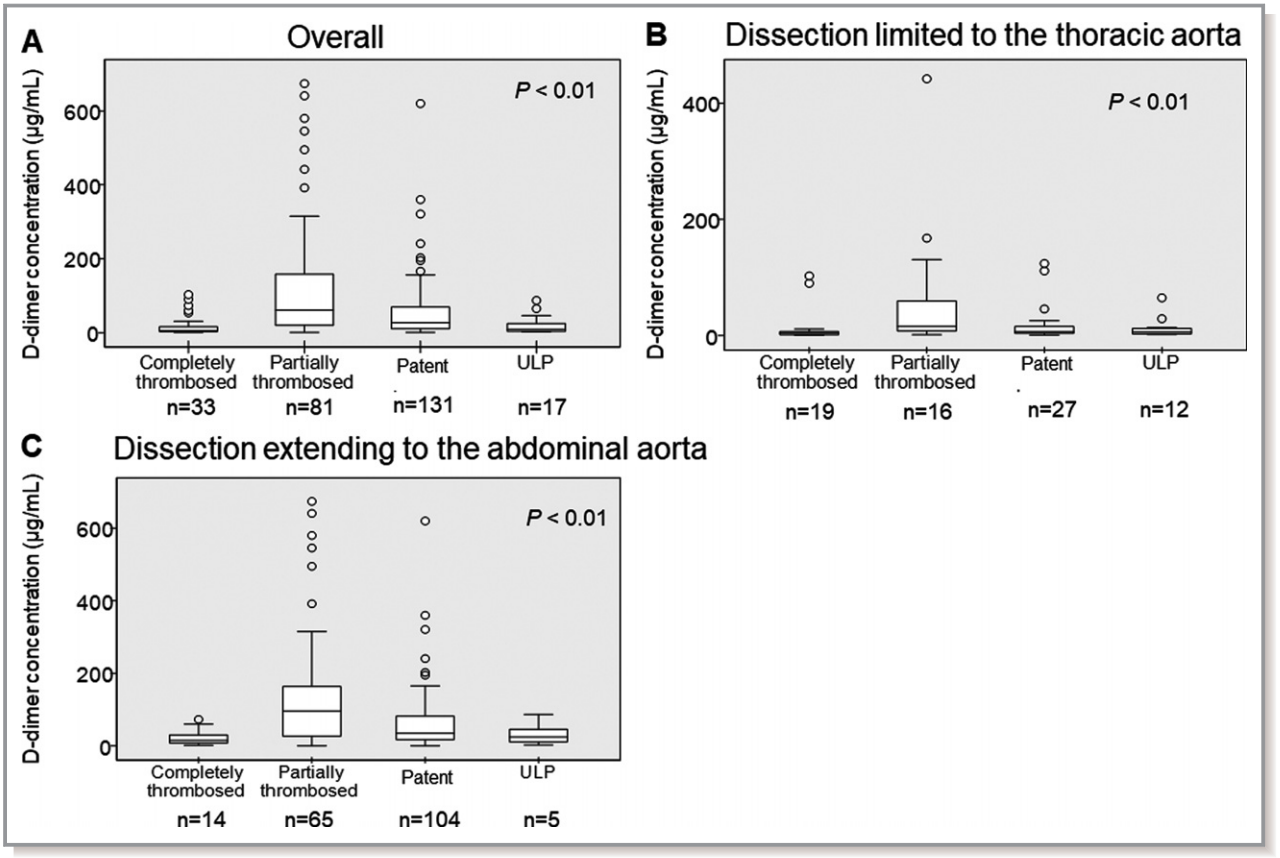

Figure 4. D-dimer concentrations assessed according to false lumen status. *P* values were obtained by Kruskal-Wallis test. A, Total patients. B, Patients with dissection limited to the ascending aorta or descending thoracic aorta. C, Patients with dissection extending below the diaphragm. ULP indicates ulcerlike projection.

ascending aorta or descending thoracic aorta, and FL status (completely thrombosed, ULP, partially thrombosed, or patent). A high D-dimer concentration (>8.3 μg/mL) was added for assessing predictors of in-hospital mortality. Between-group differences in clinical variables were analyzed by χ^2 or Fisher's exact test or by unpaired *t* or Mann-Whitney *U* test. Correlation between D-dimer concentrations and perioperative variables, including the preoperative platelet count, intraoperative blood loss volume, and transfusion volume, was assessed by Spearman's rank correlation coefficient. Freedom from time-related events (ie, death or an aortic event) was by the Kaplan-Meier method and analyzed by log-rank test. All statistical analyses were performed with SPSS 23.0 for Windows software (IBM Corp, Armonk, NY), and $P<0.05$ was considered significant.

Results

Admission D-Dimer Concentrations and Characteristics of Patients With a D-Dimer Concentration Below the Detection Limit

Distribution of the admission D-dimer concentrations among the study patients is shown in Figure 1. In calculating the median and mean D-dimer concentrations, we assigned a value of 0.5 μg/mL to any patient with a D-dimer concentration <1 μg/mL. The overall D-dimer concentration was 68.2±108.5 μg/mL, and the median (interquartile range) was 26.7 (8.3–85.9) μg/mL. Three patients (1.1%) had a D-dimer concentration that was below the detection limit (<1 μg/mL). Thus, the sensitivity of admission D-dimer for ATAAD was 98.9% (259/262). CT images from and clinical information on the 3 patients with a D-dimer concentration below the detection limit are shown in Figure S1 and Table S1, respectively. Dissection extended to the iliac artery in 2 of these patients (patients 1 and 2), and the FL of both patients was patent. Dissection was limited to the descending thoracic aorta in the third patient (patient 3), and the FL was completely thrombosed. The white blood cell count of 2 of the 3 patients (patients 1 and 3) was not elevated on admission.

D-Dimer Concentrations in Relation to Dissection Morphologic Features

D-dimer concentrations are shown in relation to the extent of dissection in Figure 3. The median (interquartile range) D-dimer concentrations were 3.9 (2.4–12.6) μg/mL for the

Table 1. Characteristics of the Total Patients and Patients per D-Dimer Concentration (≤8.3 vs >8.3 μg/mL)

Characteristics	Total (N=262)	D-Dimer ≤8.3 μg/mL (n=66)	D-Dimer >8.3 μg/mL (n=196)	*P* Value
Background				
Age, y	64.7±12.8	65.1±14.4	64.5±12.5	0.72
Sex, male	142 (54.6)	32 (48.5)	111 (56.6)	0.25
Marfan syndrome	6 (2.3)	3 (4.5)	3 (1.5)	0.35
Bicuspid aortic valve	7 (2.7)	3 (4.5)	4 (2.0)	0.52
Obesity (BMI, >30 kg/m^2)	27 (10.3)	6 (9.1)	21 (10.7)	0.71
Current smoking	80 (30.5)	17 (25.8)	63 (32.1)	0.33
Hypertension	191 (72.9)	46 (69.7)	145 (74.0)	0.49
Dyslipidemia	47 (17.9)	11 (16.7)	36 (18.4)	0.76
Diabetes mellitus	25 (9.5)	10 (15.2)	15 (7.7)	0.073
COPD	9 (3.4)	2 (3.0)	7 (3.6)	1.0
Hemodialysis	4 (1.5)	1 (1.5)	3 (1.5)	1.0
Prior cardiac surgery	2 (0.8)	0 (0)	2 (1.0)	1.0
Clinical presentation				
Symptoms				
Chest pain and/or back pain	209 (79.8)	53 (80.3)	156 (79.6)	0.90
Abdominal pain	13 (5.0)	0 (0)	13 (6.6)	0.069
Syncope	54 (20.6)	12 (18.2)	42 (21.4)	0.57
Shock (sBP, <80 mm Hg)	56 (21.4)	18 (27.3)	38 (19.4)	0.18
Severe aortic insufficiency	14 (5.3)	4 (6.1)	10 (5.1)	1.0
Organ ischemia				
Brain	35 (13.4)	4 (6.1)	31 (15.8)	0.071
Coronary	22 (8.4)	4 (6.1)	18 (9.2)	0.59
Mesenteric	15 (5.7)	1 (1.5)	14 (7.1)	0.16
Lower limb	43 (16.4)	5 (7.6)	38 (19.4)	0.025
Laboratory data				
WBC count, ×10^3/μL	12.8±6.8	13.4±10.8	12.6±4.8	0.38
Hemoglobin, g/dL	12.6±2.0	12.9±1.9	12.6±2.0	0.35
Platelet, ×10^4/μL	18.8±6.3	21.0±6.3	17.9±6.2	<0.01
AST, IU/L	54.8±96.1	63.4±106.4	51.8±92.5	0.39
ALT, IU/L	40.0±65.0	45.7±74.2	38.1±61.8	0.41
Creatinine, mg/dL	1.02±0.89	1.04±1.16	1.01±0.78	0.80
Dissection characteristics				
DeBakey classification				
Type I	239 (91.2)	51 (77.3)	188 (95.9)	<0.01
Type II	23 (8.8)	15 (22.7)	8 (4.1)	<0.01
FL status				
Completely thrombosed	33 (12.6)	20 (30.3)	13 (6.6)	<0.01
ULP-type constant enhancement	17 (6.5)	8 (12.1)	9 (4.6)	0.032
Partially thrombosed	81 (31.3)	11 (16.7)	71 (36.2)	<0.01
Patent	131 (50.0)	27 (40.9)	104 (53.1)	0.088

Continued

Table 1. Continued

Characteristics	Total (N=262)	D-Dimer ≤8.3 μg/mL (n=66)	D-Dimer >8.3 μg/mL (n=196)	*P* Value
Primary entry site*				
Ascending aorta	153 (58.4)	42 (63.6)	111 (56.6)	0.32
Aortic arch	46 (17.6)	7 (10.6)	39 (19.9)	0.086
Descending aorta or unknown	67 (25.6)	19 (28.8)	48 (24.5)	0.49

Values are mean±SD or number (percentage) of patients. *P* values were obtained by χ^2 or Fisher's exact test or by unpaired *t* test or Mann-Whitney *U* test, as appropriate. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FL, false lumen; sBP, systolic blood pressure; ULP, ulcerlike projection; WBC, white blood cell.
*Primary entry site includes multiple entry sites in some patients.

ascending aorta group (n=23), 8.1 (4.4–20.5) μg/mL for the descending thoracic aorta group (n=51), 37.8 (11.2–87.0) μg/mL for the abdominal aorta group (n=71), and 43.7 (21.7–114.4) μg/mL for the iliac artery group (n=117). The difference in D-dimer concentrations was significant (Figure 3A). In addition, D-dimer concentrations differed significantly between each of the patient groups on the basis of the extent of dissection, regardless of FL status (Figure 3B through 3D).

D-dimer concentrations are shown per FL status for the total 262 patients, for patients with dissection limited to the thoracic aorta, and for patients with dissection extending to the abdominal aorta in Figure 4. The median (interquartile range) D-dimer concentrations were 5.0 (2.6–18.0) μg/mL in the completely thrombosed FL group, 60.9 (19.4–160.4) μg/mL in the partially thrombosed FL group, 28.6 (10.0–70.9) μg/mL in the patent FL group, and 8.7 (3.2–26.9) μg/mL in the ULP-type FL group (Figure 4A). For patients with dissection limited to the thoracic aorta (Figure 4B), the median (interquartile range) D-dimer concentrations were 3.9 (1.7–8.6) μg/mL in the complete thrombosed FL group, 19.2 (8.0–65.9) μg/mL in the partially thrombosed FL group, 6.8 (3.6–18.1) μg/mL in the patent FL group, and 5.8 (3.1–13.0) μg/mL in the ULP-type FL group; these concentrations differed significantly. For patients with dissection extending to the abdominal aorta (Figure 4C), the median (interquartile range) D-dimer concentrations were 15.2 (6.9–36.3) μg/mL in the completely thrombosed FL group, 99.2 (26.2–172.5) μg/mL in the partially thrombosed FL group, 35.3 (17.3–82.9) μg/mL in the patent FL group, and 24.8 (7.0–66.6) μg/mL in the ULP-type FL group. The concentrations were markedly lower in the completely thrombosed FL group and ULP-type FL group than in the other 2 groups. The median D-dimer concentration was highest in the partially thrombosed FL group, regardless of the extent of dissection.

Patient characteristics are shown for the D-dimer ≤8.3 μg/mL group and the D-dimer >8.3 μg/mL group in Table 1. The platelet count was significantly higher and the incidence of limb ischemia was significantly lower in the D-dimer ≤8.3 μg/mL group than in the D-dimer >8.3 μg/mL group. Negative correlation was found between the D-dimer concentrations and platelet counts (Figure 5A). Brain ischemia was more common in the D-dimer >8.3 μg/mL group. Morphologic characteristics of the dissection are also shown

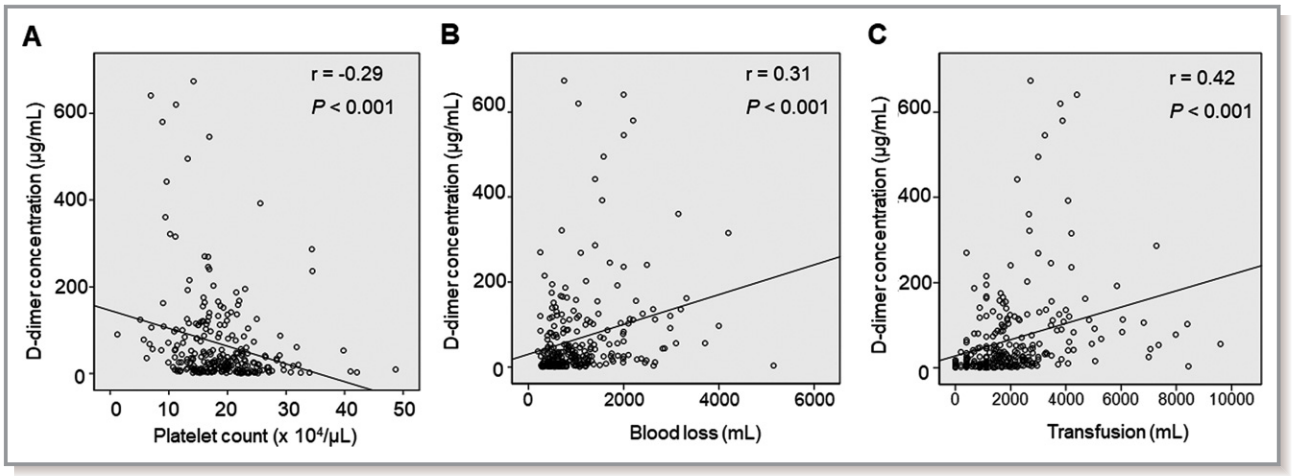

Figure 5. Correlations of D-dimer concentration and perioperative parameters. A, Platelet count. B, Intraoperative blood loss. C, Transfusion volume. *P* values were obtained by Spearman's rank correlation coefficient.

Table 2. Results of Multivariate Analysis of Predictors of a Low D-Dimer Concentration (≤8.3 μg/mL)

Variable	*P* Value	Odds Ratio	95% CI
Extent of dissection			
Ascending aorta	<0.01	9.81	3.60–26.73
Descending aorta	<0.01	7.68	3.56–16.58
Completely thrombosed FL	<0.01	4.02	1.67–9.66
Absence of brain ischemia	0.013	4.74	1.39–16.12

CI indicates confidence interval; FL, false lumen.

per group in Table 1. DeBakey type II dissection ($P<0.01$), a completely thrombosed FL ($P<0.01$), and a ULP-type FL ($P=0.032$) were significantly more prevalent in the D-dimer ≤8.3 μg/mL group than in the D-dimer ≥8.3 μg/mL group. To the contrary, a partially thrombosed FL was significantly more prevalent in the D-dimer >8.3 μg/mL group ($P<0.01$).

Multivariate analysis showed dissection limited to the ascending aorta or descending thoracic aorta, a completely thrombosed FL, and absence of brain ischemia to be predictors of a low D-dimer concentration (Table 2).

Operative Variables and Admission D-Dimer Concentrations in Relation to Outcomes of ATAAD

To understand admission D-dimer concentrations in relation to outcomes of surgically treated ATAAD, we examined early and late outcomes among patients with a D-dimer concentration ≤8.3 mg/mL and those among patients with a D-dimer concentration >8.3 μg/mL and then compared outcomes between the 2 groups. Operative variables and early hospital outcomes are shown in Table 3. There was no between-group difference in proximal reconstruction procedures. For the extent of aortic resection, patients in the D-dimer >8.3 μg/mL group were more likely to have undergone aortic arch replacement. Operation time, the intraoperative blood loss volume, and operative transfusion volume were significantly greater in the D-dimer >8.3 μg/mL group than in the D-dimer ≤8.3 μg/mL group ($P<0.01$ for all). Positive correlations were found between D-dimer concentrations and intraoperative blood loss volume and transfusion volume (Figure 5B and 5C). Resection of the primary entry tear, cardiopulmonary bypass time, myocardial ischemia time, and nadir intraoperative body temperature did not differ between the groups.

Early outcomes were as follows: in-hospital mortality was 8.8% (23/262) for the total patients, 1.5% (1/66) for the D-dimer ≤8.3 μg/mL group, and 11.2% (22/196) for the D-dimer >8.3 μg/mL group ($P=0.031$). The incidences of new postoperative onset stroke and reexploration for bleeding were higher in the D-dimer >8.3 μg/mL group than in the D-dimer ≤8.3 μg/mL group, but the differences were not statistically significant. Multivariate analysis showed shock (systolic blood pressure, <80 mm Hg), obesity (body mass index, >30 kg/m^2), prior cardiac surgery, brain ischemia, mesenteric ischemia, and D-dimer >8.3 μg/mL to be predictors of in-hospital mortality (Table 4).

Late outcomes of the patients who were discharged from the hospital are shown in Figure 6. Seven-year survival was 93.4±3.9% in the D-dimer ≤8.3 μg/mL group and 77.5±5.8% in the D-dimer >8.3 μg/mL group ($P=0.14$). Seven-year freedom from an aortic event was 88.5±4.1% for the D-dimer ≤8.3 μg/mL group and 82.2±5.0% for the D-dimer >8.3 μg/mL group ($P=0.88$). Twenty-three patients died during follow-up, 3 in the D-dimer ≤8.3 μg/mL group and 20 in the D-dimer >8.3 μg/mL group. The details of late mortality are shown in Table S2. The incidence of late death did not differ significantly between the 2 groups.

Discussion

Previously reported studies of the relation between serum D-dimer concentrations and dissection morphologic features have included relatively small numbers of patients (n=24–114) and have not controlled for the time from symptom onset to hospital admission.[12–15] To the best of our knowledge, the study described herein is the largest to date in which the relation between D-dimer concentrations and dissection morphologic features has been examined in patients who have undergone aortic repair for ATAAD. We focused the investigation on the early phase of the disease (within the first 24 hours after symptom onset) so that our overall study group would be fairly homogeneous. The key findings were that patients' admission D-dimer concentration was reflective of both the extent of aortic dissection and status of the FL. The D-dimer concentration was higher in patients with dissection that extended below the level of the diaphragm than in patients with dissection that did not extend this far. Similarly, the D-dimer concentration was higher in patients with a partially thrombosed or patent FL than in those with a completely thrombosed FL. Consistent with these findings, dissection limited to the ascending aorta or descending thoracic aorta and a completely thrombosed FL were identified as predictors of a low D-dimer concentration. In comparison to patients with a low D-dimer concentration, patients with a concentration >8.3 μg/mL had a relatively low preoperative platelet count, required a relatively large volume of transfused blood, and underwent a relatively prolonged operation. The higher D-dimer concentration was associated with increased in-hospital mortality but was not related to late outcomes.

Table 3. Operative Variables and Short-Term Outcomes of the Total Patients and per D-Dimer Concentration (≤8.3 vs >8.3 μg/mL)

Variables	Total (N=262)	D-Dimer ≤8.3 μg/mL (n=66)	D-Dimer >8.3 μg/mL (n=196)	*P* Value
Operative variables				
Proximal reconstruction				
Valve resuspension	233 (88.9)	56 (84.8)	177 (90.3)	0.22
Modified Bentall	13 (5.0)	5 (7.6)	8 (4.1)	0.98
Valve conservative root surgery	2 (0.8)	2 (3.0)	0 (0)	0.10
Isolated aortic valve replacement	14 (5.3)	3 (4.5)	11 (5.6)	0.98
Distal extent of aortic resection				
Ascending aorta or hemiarch	210 (80.2)	59 (89.4)	151 (77.0)	0.030
Aortic arch	52 (19.8)	7 (10.6)	45 (23.0)	0.030
No open stent insertion	41 (15.6)	6 (9.1)	35 (17.9)	0.090
Open stent insertion	11 (4.2)	1 (1.5)	10 (5.1)	0.37
Resection of the primary entry	185 (70.6)	44 (66.7)	141 (71.9)	0.42
Operation time, min	325 (261–414)	286 (233–361)	340 (277–431)	<0.01
CPB time, min	161.5±74.5	148.0±54.6	166.0±79.7	0.089
Myocardial ischemia time, min	107.6±49.6	103.9±47.8	108.8±50.2	0.49
Blood loss, mL	820 (538–1315)	650 (448–1000)	925 (583–1573)	<0.01
Transfusion, mL	1720 (1120–2680)	1120 (640–1960)	1880 (1140–3000)	<0.01
Lowest body temperature, °C	21.7±2.9	22.0±3.1	21.6±2.8	0.27
Short-term outcomes				
In-hospital death	23 (8.8)	1 (1.5)	22 (11.2)	0.031
Death within 30 d of surgery	18 (6.9)	1 (1.5)	17 (8.7)	0.088
Complications				
New-onset postoperative stroke	20 (7.6)	1 (1.5)	19 (9.7)	0.058
Prolonged ventilation >48 h	131 (50.0)	29 (43.9)	102 (52.0)	0.25
Reexploration for bleeding	11 (4.2)	0 (0)	11 (5.6)	0.11
Mediastinitis	5 (1.9)	0 (0)	5 (2.6)	0.43
Renal replacement therapy	25 (9.5)	4 (6.1)	21 (10.7)	0.38

Mean±SD, or median (quartile 1–quartile 3), or number (percentage) of patient values are shown. *P* values were obtained by χ^2 or Fisher's exact test or by unpaired *t* test or Mann-Whitney *U* test, as appropriate. CPB indicates cardiopulmonary bypass.

The clinical manifestations of AAD vary at the time of presentation, depending on the organ or organs affected by the ischemia and whether hemodynamic instability is present. Imaging is necessary for a definitive diagnosis, but it is sometimes difficult to judge whether contrast-enhanced CT should be performed for patients without typical symptoms. Integrated approaches to the diagnosis of acute aortic pathologic features are needed. The efficacy of D-dimer as a biomarker for AAD has been studied extensively on the background of such clinical demands. Although we applied 1 μg/mL (1000 ng/mL), 0.5 μg/mL has been more frequently used as a cutoff for diagnosis of AAD.[6,8,9,28] Meta-analyses examining 0.5 μg/mL as the cutoff value showed that D-dimer has high sensitivity, ranging between 95% and 98%,[6,8,9,28] but only 40% to 60% specificity.[6,8,9] D-dimer has been considered a sensitive but nonspecific marker for AAD. However, recent retrospective[7] and prospective[10] studies showed that if used in combination with an aortic dissection risk scoring system, D-dimer testing has negative predictive values as high as 98.9%[7] and 99.7%[10] in patients with AAD. We believe such a combination of tests will become the standard diagnostic approach used to confirm or rule out AAD.

The usefulness of D-dimer as a marker of disease activity has been investigated in other maladies. In patients with pulmonary embolism, the D-dimer concentration is related to

Table 4. Results of Multivariate Analysis of Predictors of In-Hospital Mortality

Variable	*P* Value	Odds Ratio	95% CI
D-dimer >8.3 μg/mL	0.033	11.83	1.21–115.53
Shock (sBP, <80 mm Hg)	<0.01	22.11	5.27–92.74
Obesity (BMI, >30 kg/m^2)	<0.01	33.21	6.70–164.49
Prior cardiac surgery	<0.01	137.06	6.04–3109.48
Mesenteric ischemia	<0.01	11.74	2.27–60.69
Brain ischemia	<0.01	6.95	1.83–26.34
Hemodialysis	0.089	12.95	0.68–248.14

BMI indicates body mass index; CI, confidence interval; sBP, systolic blood pressure.

thrombus volume assessed by contrast-enhanced CT,[29] and a high D-dimer concentration of >5000 ng/mL is a risk factor for in-hospital mortality.[30] Similarly, in patients with deep vein thrombosis, the ultrasound-based estimated thrombus volume correlates with the D-dimer concentration.[31] These findings are consistent with the finding that D-dimer elevation is associated with extensive aortic dissection.[12–14] The insight gained from our study is that the D-dimer concentration is related to the extent of dissection in patients with ATAAD regardless of the FL status. Patients with intramural hematoma-type dissection are reported to have a relatively low D-dimer concentration.[12,15] We confirmed that the D-dimer elevation is milder in patients with a completely thrombosed FL or a ULP-type FL than in patients with a patent FL. In cases of AAD, D-dimer is produced in the FL of the dissecting aorta. Release into the systemic circulation may result in D-dimer elevation in patients with a patent FL. The D-dimer concentrations were highest in our patients with a partially thrombosed FL, regardless of the extent of dissection. Nagaoka et al[32] reported an elevated fibrinogen degradation products concentration in patients with acute type B aortic dissection and a partially thrombosed FL (n=14; median, 18.8 μg/mL) in comparison to that in similar patients with a patent or thrombosed FL (n=21; median, 5.5 μg/mL) (*P*=0.01). Thrombogenicity of a partially thrombosed FL, in comparison to that of a patent FL, may be greater, and fibrinolytic activity may thus be markedly enhanced.[32]

D-dimer elevation may be seen in conditions in which fibrin is formed and then broken down, including such conditions as recent surgery, arrhythmia, pregnancy, trauma, infection, heart attack, and some cancers or conditions in which fibrin is not cleared normally, such as liver cirrhosis.[5] The behavior of D-dimer should be understood when the data are being

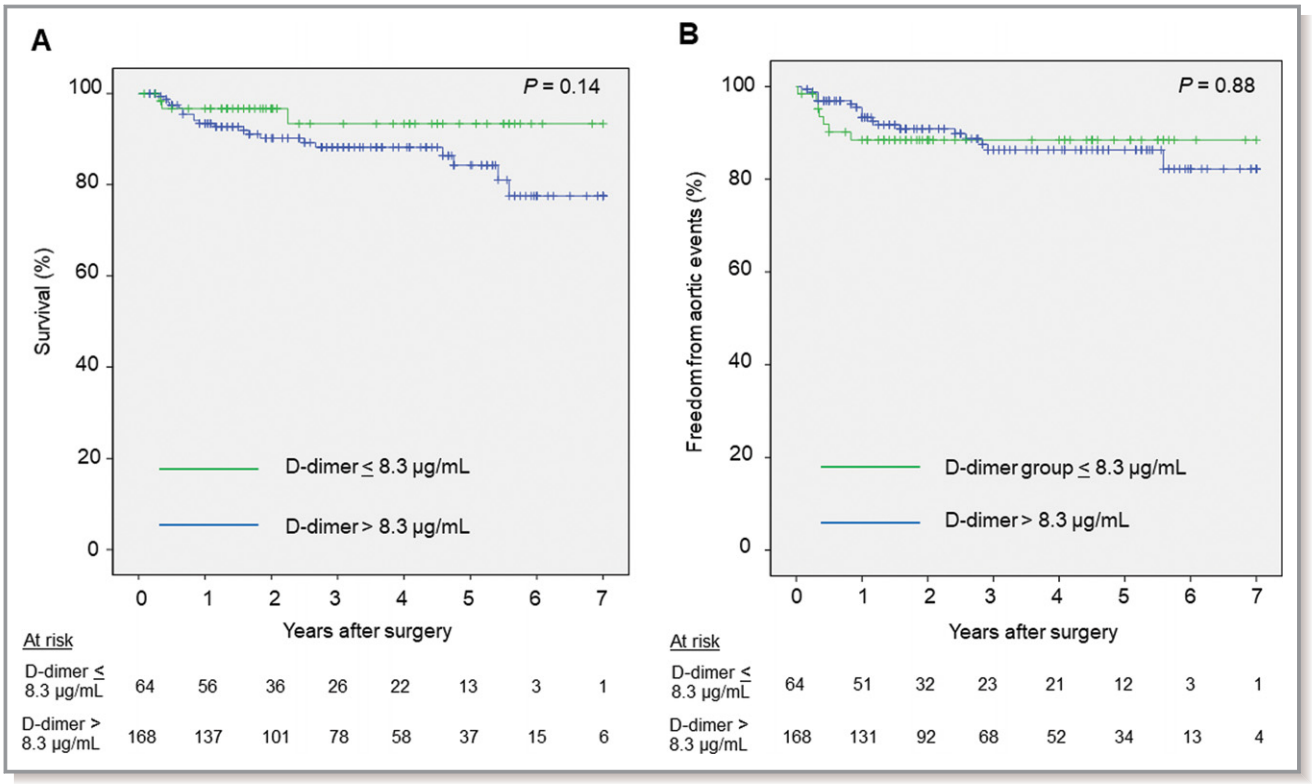

Figure 6. Kaplan-Meier curves for late survival (A) and freedom from an aortic event (B) for patients with acute type A aortic dissection with an admission D-dimer concentration ≤8.3 μg/L and those with an admission D-dimer concentration >8.3 μg/L. *P* values were obtained by log-rank test. The 23 patients who died in the hospital after aortic repair were excluded from this analysis. The follow-up rate was 96.6% (231/239).

interpreted. In addition to dissection morphologic features, age[12] and the time between the onset of symptoms and D-dimer testing[14,33] have been reported to influence the D-dimer concentration. The serum D-dimer concentration has been reported to increase within 6 hours after the onset of aortic dissection and to peak within 24 hours.[20,33] D-dimer has a half-life of ≈8 hours.[5] Although the sensitivity of D-dimer testing remains high at 95.3% up to 10 days after the onset of AAD,[34] delayed hospital arrival may influence the D-dimer concentration, possibly obscuring the telltale elevation.

D-dimer has recently gained attention as an outcome predictor for patients with AAD.[13,21–23] Wen et al (cutoff, 5.67 μg/mL)[22] and Gorla et al (cutoff, 9.0 μg/mL)[23] reported that a D-dimer concentration above the cutoff level was a risk factor for in-hospital mortality in patients with ATAAD or acute type B aortic dissection. Huang et al (cutoff, 6.1 μg/mL) also reported that a D-dimer concentration above the cutoff level was a risk factor for both in-hospital and long-term mortality among patients with ATAAD, including some who underwent conservative therapy.[21] We excluded from our study patients who underwent conservative therapy so that we could investigate the relation between admission D-dimer concentrations and surgical outcomes. We found greater hospital mortality among patients with a D-dimer concentration above our cutoff of 8.3 μg/mL than among those with a lower concentration. A possible explanation is the fact that patients with a relatively high D-dimer concentration are more likely than others to have experienced organ ischemia, probably because of more extensive dissection. In addition, surgery for patients with a relatively high D-dimer concentration tends to be significantly prolonged, and the transfusion volume is increased (despite lack of differences in cardiopulmonary bypass times and intraoperative temperature nadir). We consider the lower preoperative platelet count to have been associated with intraoperative coagulopathy in the D-dimer >8.3 μg/mL group. In contrast to early outcomes, late outcomes did not differ between our groups. Song et al[19] reported that partial FL thrombosis after initial aortic repair leads to aortic enlargement in patients with DeBakey type I ATAAD. Among our patients, those with a partially thrombosed FL had the highest admission D-dimer concentrations; however, FL status can be altered by aortic repair. A further study in which the D-dimer concentration is measured postoperatively is needed to investigate the utility of D-dimer for prediction of late outcomes in patients with ATAAD.

Our study data should be evaluated in light of the study limitations. The study was conducted at a single center in a retrospective manner. In addition, the monoclonal antibody used in a D-dimer assay recognizes a specific epitope on the D-dimer fragment, but there are >20 different monoclonal antibodies used for 30 different D-dimer assays.[5] Furthermore, antibodies have different analytical sensitivities and specificities.[5] Although we used 8.3 μg/mL as a cutoff for the low/relatively high D-dimer concentration, on the basis of previous studies and on the distribution among our patients, lack of standardization of D-dimer assay could have led to selection bias. A standardized D-dimer testing system is desirable for future multicenter prospective study. Finally, we did not use 0.5 μg/mL, a generally accepted cutoff for D-dimer testing of AAD, because of the measurement system we used.

In conclusion, the admission serum D-dimer concentration can be strongly influenced by the extent of dissection and FL status in patients with ATAAD. The concentration will be relatively high in patients with a partially thrombosed FL and low in patients with a completely thrombosed FL or a ULP-type FL, regardless of the extent of dissection. A relatively high admission D-dimer concentration appears to be associated with a decreased platelet count, increased operative transfusion volume, and relatively prolonged operation, possibility leading to in-hospital mortality. Thus, operative risks are increased in patients with a relatively high D-dimer concentration. Recognition of these clinical and morphologic features in the context of D-dimer testing can lead to accurate diagnosis and help surgeons optimize the perioperative management of patients with ATAAD.

Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Patients with a Serum D-Dimer Concentration <1 μg/Ml.

Patient	Time from symptom onset to hospital arrival	Comorbidity	Admission WBC count	Extent of dissection	Diameter of ascending aorta	FL status	Hemodynamic status/organ ischemia	Location of the intimal tear	Surgery/ outcome
#1 42-year-old male	2.5 hours	HTN	6,930/μL	Iliac artery	51 mm	Patent	Stable/limb	Ascending aorta and aortic arch	Valve sparing root surgery, TAR with OS/ discharged
#2 73-year-old female	23 hours	HTN, diabetes, dyslipidemia, IHD	13,570/μL	Iliac artery	47 mm	Patent	Stable/ coronary, limb	Descending thoracic aorta	HR, CABG/ discharged
#3 78-year-old female	6 hours	CVD	6,450/μL	Descending thoracic aorta	45 mm	Completely thrombosed	Stable/none	Not identified	HR/ discharged

WBC indicates white blood cell count; FL, false lumen; HTN, hypertension; IHD, ischemic heart disease; CVD, cerebrovascular disease; TAR, total arch replacement; OS, open stent; HR, hemiarch replacement; CABG, coronary artery bypass grafting.

Table S2. Causes of Late Mortality in the Total Patients and Per D-Dimer Concentration (≤8.3 μg/mL vs. >8.3 μg/mL).

	Total patients (n=23)	D-dimer ≤8.3 μg/mL (n=3)	D-dimer >8.3 μg/mL (n=20)	*P* value
Pneumonia	5 (21.7%)	0 (0%)	5 (25.0%)	0.82
Heart failure	4 (17.4%)	0 (0%)	4 (20.0%)	0.97
Malignancy	4 (17.4%)	1 (33.3%)	3 (15.0%)	1.0
Aortic rupture	2 (8.7%)	1 (33.3%)	1 (5.0%)	0.59
Cerebrovascular disease	2 (8.7%)	1 (33.3%)	1 (5.0%)	0.59
Renal failure	2 (8.7%)	0 (0%)	2 (10.0%)	0.48
Unknown	4 (17.4%)	0 (0%)	4 (20.0%)	0.97

Figure S1. Computed tomography images of the 3 patients with an admission D-dimer concentration <1 μg/mL.